Biomarker Profiles and Immunologic Predictors of Neurodevelopment in Children who are HIV Exposed Uninfected

Ashley Egler[1], Jeong Hoon Jang[2], Wei Li[3], Megan McHenry[4], Eren Oyungu[5], Qigui Yu[3], Alka Khaitan[4]

1. Indiana University School of Medicine 2. Indiana University School of Medicine, Department of Biostatistics & Health Data Science 3. Indiana University School of Medicine, Department of Microbiology & Immunology 4. Indiana University School of Medicine, Department of Pediatrics 5. Moi University, College of Health Sciences, School of Medicine, Eldoret, Kenya

Background: Children who are HIV-exposed uninfected (HEU) have higher morbidity and mortality rates than their unexposed uninfected counterparts (HU). HEU also exhibit lower neurodevelopmental outcomes. Previous studies show that HIV-induced immune dysregulation can be linked to decreased neurodevelopment in HIV+ children. However, the role of inflammation on neurodevelopment in HEU remains unclear.

Methods: This study investigated the plasma levels of 81 biomarkers in 82 Kenyan children between the ages of 18 and 36 months. Neurodevelopment was measured using the Bayley Scales of Infant and Toddler Development, 3rd edition. Bayesian model averaging was used to identify significant biomarkers.

Results: HEU showed lower levels of 12 different proinflammatory cytokines/chemokines/growth factors: IL-12, leukemia inhibitory factor (LIF), macrophage migration inhibitory factor (MIF), TNF-related weak inducer of apoptosis (TWEAK), and A proliferation inducing ligand (APRIL); BLC, eoxtaxin-2, I-TAC, monokine induced by gamma interferon (MIG), and MIP-3a; fibroblast growth factor-2 (FGF-2) and granulocyte colony-stimulating factor (G-CSF). HEU showed higher levels of 2 inhibitory soluble immune checkpoints: T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and CD40. Bayesian model averaging identified the biomarkers to best predict HEU vs. HU status were IL-12, IL-13, and CD40. In HU children, hepatocyte growth factor (HGF) and IL-5 predicted cognitive scores, BLC and IL-7 predicted motor outcomes, and IL-1a, IL-2R, IL-5, and maternal education predicted language scores. In HEU, FGF-2 predicted language scores, and IL-22 predicted motor development. Statistical analysis identified IL-2R and IL-22 as the strongest predictors of neurodevelopmental outcomes in HU and HEU, respectively.

Conclusion/Potential Impact: This study shows that HEU exhibit an immune suppressive biomarker profile, rather than an inflammatory profile as indicated in previous studies. The significant biomarkers we found may be used to determine children at risk of decreased poor neurodevelopmental outcomes, allowing more time for intervention.